RESPIRATORY MEDICINE (1999) 93, 220–223

Letters to the Editor

Dear Editor

A critical reappraisal of transmission routes for bovine TB in cattle

The global resurgence of human TB may be exacerbated by an increasingly important role of avian and bovine TB, since immunocompromization may become widespread due to HIV as well, perhaps, as the alarming but insidious spread of other causes such as man-made organo-chlorine/phosphorus compounds (i.e. dioxins, PCBs and OP pesticides which may be a factor in BSE) (1). And yet, even for human TB, transmission risk factors need clarification. Many famous authors and composers succumbed to the disease, for example the Brontës, Chopin, Keats and Shelley, but their relatives and friends in daily nursing contact failed to catch TB. Stress, such as a prison environment, may increase risk, as with Nelson Mandela (2). Classic studies suggested that in man, respiratory consumption or adult phthisis was distinct from dietary childhood scrofula from milk, but major disagreement persisted over the inhalation/ingestion role in cattle (3–6).

Worldwide cattle TB eradication schemes based on test/slaughter have been very successful, but incidences of failure have controversially been blamed on a wildlife source rather than mistested/untraced cattle; Anglo-Irish badgers or possums and ferrets in New Zealand [7–10 (p. 152)]. It remains unclear after 2·5 decades of wildlife culling at great expense, whether these species are merely a spill-over host from cattle, or whether they really can transmit bovine TB to cattle. New hi-tech studies using DNA typing may provide some answers, in that badger/cattle strains are often the same, but this may not prove which was the originator; indeed in three out of nine cases in one study, badgers could not have been the source (10,11)! Hence, it is perhaps worthwhile reappraising the long-neglected but immense amount of empirical work in the classic reviews on 'old-fashioned' lymph-node drainage from entry sites, experimental infection, etc (3–6) to shed light on relative aetiopathogenetic risk factors.

Cattle are the natural and ideal maintenance host for the obligate parasite of bovine TB and whilst most transmission, as in man, is via either respiratory or alimentary consumption/scrofula, the evolutionary arms race between host and parasite has resulted in a fine balance in which three key factors must be present if transmission is to occur. Unlike man, cattle are infectious at any stage of the disease. Although few bacteria may be shed from early non-visible lesion (NVL) cases, gross VL cases can shed 38 million bacilli per day in 30 lbs of faeces. The VL stage may take months to develop, but the process can be as rapid as 1–2 months (10,12,13). The strain, virulence, challenge dose and route of entry are critical. Thirdly, the recipient must be susceptible, which can involve genetic or acquired immunity or resistance. A minimum challenge dose is needed 'on average' (14,15), as is also true for badgers (16). West African Dama and Zebu breeds seem more resistant than Jersey/Guernsey breeds, although the alleged insusceptibility of some hardy breeds may be due to overwintering outdoors (Kyloe, Shorthorns), whereas Friesians and other breeds wintered in yards or sheds can pick up TB indoors, leading to a resultant spring peak of TB. Some immunity due to continuous subclinical challenge from pre-War unpasteurized milk in man contrasts with complications such as immunocompromization from silicosis in man and badgers (4). The immune response is both cellular and humoral and this may be an eventual basis for more effective cattle testing using a single blood sample, which would speed up removal of TB cases (14,15), but the aetiology may be obscured by such complexity. The spread of neutrophil leucocytes within the body may be crucial as loss of plasticity of cell walls may stop them squeezing through micro-capillaries. Cell death with its consequent lysis and shedding of phagocytosed bacteria then sets up a new 'lesion focus' in any richly vascularized tissue such as the lung, brain meninges or bone, and the kidneys in badgers (4,5,17).

The classic studies by Francis (3,4) concluded that 80–90% of cattle TB was of respiratory origin. Based on retropharyngeal lymph node studies, some 11·7% of bovine TB was dietary in origin but interestingly the reverse was found for facultatively parasitic and environmentally ubiquitous avian TB: 9·6% of inhaled origin versus 90·4% of ingested origin. Other routes, such as congenital, milk, stud bulls, iatrogenic, constituted 1% of transmission but today, as overt clinical TB of the udder, uterus, etc is rare, transmission is almost completely aerogenous. Francis provided invaluable information on the relative risks via these two main routes. Thus, whilst Chaussé found that as few as six bacilli might be enough for transmission via the aerogenous route, aerosolized sputum or faecally contaminated dust particles over 10 μm in size may not be able to penetrate to the innermost alveoli and achieve infection (4). Inquisitive nosing may be enough to pass TB between contiguous herds (18), but surprisingly even when calves are confined with excreting cattle they may not become infected (Neill, cited in 19). Other Irish studies found that TB did not spread easily amongst herds (20), but the explanation for this may be, as noted by Francis, that very close 'contact' over time may be needed, such that heifers did not get TB until they entered the cowshed for their first calf and young stock, in particular beef cattle, kept outdoors may stay TB-free (3,4). Contaminated fine dust may perhaps be

0954-6111/99/030220+04 $12.00/0

more important than sputum droplets. A badger to calf transmission experiment failed with exposure of only 1 month and took far longer than expected (6 months) for the rest (16). The often-cited view that badger urine containing 300,000 bacilli ml^{-1} might pass TB to cattle by eructation (burping) of rumen gases into the lungs seems likely to pose an inadequate challenge dose via this 'pseudo-respiratory' route (19,21,22).

Dietary TB in cattle might entail three main routes: via milk, water and faeces. However, transition via this route is 100 to 1 million times more difficult than via the respiratory route. Schroeder at the turn of the century, suggested that one drink of tuberculous milk might suffice for transmission, but Adami's study failed to show transmission of TB to calves after 5 months' exposure and it seems that a dose of over 300,000 bacilli ml^{-1} of milk may be necessary for infection (4,5,23). The above-mentioned badger urine bacterial count seems improbable as a source, as most urine will be lost in soil or vegetation, be disinfected within hours by UV light from sunlight, and anyway is avoided by most cattle (19). Bacilli may survive for 5 months in slurry, 7 months in water, or for approximately 1 year under cow-pats (24), thus in arid areas waterholes may be a significant point source of TB amongst bovines (4). Similarly, watercourses contaminated by slurry may be significant in affecting herds pastured downstream and farm ponds have historically been fenced off to keep cattle away from infectious organisms associated with yard drainage such as TB and *Salmonella*.

Although cattle faeces or slurry may contain massive numbers of bacilli, two classic studies showed that transmission to healthy stock only occurred within 1–2 weeks of super-contamination of pasture [Maddock (1936) and Schnellner (1959), cited in 3, 6, 19]. Leaving pasture ungrazed for 1 month often sufficed to prevent re-infection of stock. Also, 10 mg of faeces may be required to infect a calf, *in vitro* probably several thousand million bacilli or several pounds of faeces from a heavily infected cow which is unlikely in the field, this amounts to several litres of badger urine (3)! It is interesting that selective grazers such as rabbits and sheep seldom are infected with bovine TB, although sheep may catch TB when housed in sheds (4). In contrast badgers and pigs may be infected with TB from 'dirty feeding' on pasture (4,5,8). Both badgers and pigs can pick up avian TB, as can cattle, and of the few cases of TB in wild deer, the disease is often avian TB in the retropharyngeals. It seems feasible that in cattle TB areas, deer might get bovine TB e.g. from water troughs (red, sika, roe and fallow deer). The first wild TB-infected badgers probably caught bovine TB via roe deer carrion as an overspill to final cattle TB eradication in the 1950s in Switzerland. Most carnivores seem prone to acquiring TB from meat, including farmed mink and foxes, big cats in zoos and ferrets feed on possum carrion from cattle TB areas, which seems the most likely route of infection for New Zealand ferrets rather than transmission from ferrets to cattle (4,9,19). The conclusion that badgers are unlikely to pass TB to cattle seems inescapable. The dozen or so documented cases of a terminally tuberculous badger in a barn might realistically have caused the herd breakdown, but such cases account for under 1% of 5000 breakdowns over a 20-year period. Transmission from possums in New Zealand remains unclear, but cattle nosing or licking possums dying on pasture with open skin lesions might be a plausible transfer route (19,25).

There is very little spread of TB either within or between known infected badger social clans (8,10). There is some evidence, however, that much transmission may be via close social contact, particularly 'pseudo-vertically' between the sow and cubs which keeps TB going between generations. TB in cattle also seems to run in sub-familial groups within herds and the fact that isolated breakdowns often involve one VL cow and one to two inconclusive reactors suggests that odd individuals may be particularly susceptible, and/or super-excretors, which exacerbates the difficulty of eradicating TB.

Finally, one aspect of TB in wildlife which has been greatly overlooked is that such species may be passive vectors. Given a major self-maintaining reservoir of TB in cattle, it seems inevitable that wildlife may spread TB further afield. This may be particularly important amongst loose herd clusters and in closed herds (7). Whilst the difficulty of achieving a minimum challenge dose for cattle remains, it seems at least feasible that this does occasionally occur. Thus, starlings, like badgers, turn over cow-pats in search of grubs, beetles and worms and may then visit cattle food areas or troughs. They have been suspect for the spread of diseases such as *Salmonella* and foot and mouth disease, indeed the birds' faeces still contained foot and mouth virus 24 h after ingestion. Many birds and bats feed on dung beetles and even barn-nesting swallows, which eat *Aphodius* sp., have been implicated in *Salmonella* spread. Wood pigeons may feed on cattle feed areas and contaminated pasture, as well as sharing water troughs (4). Gulls, too, go 'worming' on pasture and may spread botulism to reservoirs. Rats do not develop lesions, but can be lifetime carriers of TB for approximately 1 year and their faeces in food troughs may form a frass with cattle cake dust which can be inhaled by stock. Lastly, ticks and fleas have received little attention as vectors of TB for badgers or cattle but could, in rare circumstances, be involved in transmission (26,27). In conclusion, it seems likely that badgers may pick up TB, *Salmonella*, brucellosis, etc from cattle, but are dead-end hosts unlikely to pass infection back to stock (28).

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Dear Editor

Does an inhaled β-adrenergic or anticholinergic agent improve gas exchange at rest and during exercise in patients with COPD?

In a recent issue of *Respiratory Medicine* (1), Patkas *et al.* have reported that salmeterol or ipratropium bromide produces significant improvement in airway obstruction in the recovery of post-exercise HbO_2 desaturation and in dyspnoeic sensation in patients with chronic obstructive pulmonary disease (COPD). We basically agree with the authors that both inhaled agents, i.e. salmeterol (a β-adrenergic agent) and ipratropium bromide (an anticholinergic agent), are very beneficial in terms of reducing breathlessness and improving the exercise performance in patients with COPD. The current observations were in agreement with the data from our and previous other studies (2–7). However, gas exchange before and after administration of the bronchodilatory agents in patients with asthma and COPD is still a matter of debate. Gross and Bankwala demonstrated that nebulised atropine methonitrate (an anticholinergic agent) had no significant effect on gas exchange in hypoxaemic patients with COPD; however, metaproterenol hydrochloride elicited a significant decrease in PaO_2 (8). Igarashi *et al.* have reported that fenoterol (a β-adrenergic agent) and oxitropium bromide (an anticholinergic agent) improved FEV_1 by 21 and 16% in COPD patients without hypoxaemia, respectively, and that the mean value of PaO_2 decreased from 74·5 to 69·3 torr with fenoterol, but not with oxitropium and placebo (9). The current study further indicates that nadir SaO_2 and the recovery of post-exercise hypoxaemia are better after inhalation of an anticholinergic agent than those after inhalation of a β-adrenergic agent in patients with stable COPD. These observations suggest that an inhaled anticholinergic agent is more favourable for patients with COPD than a β-adrenergic agent from the viewpoints of gas exchange at rest and during exercise.

Finally, analytical indices such as BS_{max}, TLD, BLD, and the recovery time for SaO_2 in the current study were fairly similar to those determined in our studies (2–4,10). Although the methodology was different (the current study used a walking test and our study used a cycle ergometer), the concepts should be more appropriately quoted. As one of the major goals of bronchodilator therapy in patients with COPD may be to relieve dyspnoea on exertion, we believe that the quantitative parameters for assessment of dyspnoea should be carefully and widely used in the clinical setting.

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